

Vinyl bromide; CASRN 593-60-2

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

STATUS OF DATA FOR Vinyl bromide

File First On-Line 05/01/1993

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	05/01/1993
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Vinyl bromide
CASRN — 593-60-2

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Vinyl bromide
CASRN — 593-60-2
Last Revised — 05/01/1993

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Hypertrophy, basophilic and eosinophilic foci, in the liver	NOAEL: None NOAEL(ADJ): None NOAEL(HEC): None	3000	1	3E-3 mg/cu.m
Chronic Rat Inhalation Study	LOAEL: 43 mg/cu.m (9.7 ppm) LOAEL(ADJ): 7.7 mg/cu.m LOAEL(HEC): 7.7 mg/cu.m			
Benya et al., 1982; Busey, 1979				

*Conversion Factors and Assumptions — MW = 106.9. Chamber temperature reported as 21 C and assuming 760 mmHg, LOAEL (mg/cu.m) = 9.7 ppm x 106.9/24.12 = 43. LOAEL(ADJ) = 43 x 6 hours/24 hours x 5 days/7 days = 7.7 mg/cu.m. The LOAEL(HEC) was calculated for a gas:extrarespiratory effect assuming periodicity was attained. For the rat, b:a lambda(a) = 4.05, for the human, b:a lambda(h) = 2.27 (Gargas et al., 1989). Since b:a lambda(a) is greater than b:a lambda(h), a default value of 1 is used for this ratio. LOAEL(HEC) = LOAEL(ADJ) x (b:a lambda(a)/b:a lambda(h)) = 7.7 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

Benya, T.J., W.M. Busey, M.A. Dorato, and P.E. Berteau. 1982. Inhalation carcinogenicity bioassay of vinyl bromide in rats. *Toxicol. Appl. Pharmacol.* 64(3): 367-379.

Busey, W.M. 1979. Oncogenic potential of vinyl bromide during chronic inhalation exposure - rats: Pathology Report. EPA/OTS 8EHQ-0479-0281.

The interim and final results from a chronic study of vinyl bromide inhalation in rats were reported in several reports (Busey, 1978, 1979; Huntington Research Center, 1977a,b) and in a peer-reviewed publication (Benya et al., 1982). In this study, male and female Sprague-Dawley rats were exposed to target concentrations of 0, 10, 50, 250, and 1250 ppm [actual concentrations were 0, 9.7, 52, 247, or 1235 ppm (0, 43, 230, 1095, or 5474 mg/cu.m), respectively] vinyl bromide vapor for 6 hours/day, 5 days/week (duration adjusted to 0, 7.7, 41, 196, or 977 mg/cu.m) for 6, 12, 18, or 24 months. Chamber temperature was maintained at 21 C. Initial group sizes were 120/sex in the exposed groups and 144/sex in the control group. Five rats from each group were sacrificed at 6 months, and 10 from each group were sacrificed at 12 and 18 months. All rats surviving for 24 months were sacrificed at that time, with the exception of the 1250-ppm group, which was sacrificed at 18 months due to high mortality. Parameters monitored included clinical signs, body weight, hematology, blood chemistry, urinalysis, organ weights, gross pathology, and histopathology, including brain, gonads, kidneys, liver, heart, lungs, trachea, spleen, and thyroid. The nasal cavity was not examined histologically.

Serum bromide levels were determined only for the two highest exposure groups and were elevated. Little difference was observed in the serum bromine levels between groups exposed to 250 or 1250 ppm vinyl bromide, consistent with other data showing that saturation of metabolism occurs in rats at approximately 50 ppm (Filser and Bolt, 1979). Reduced RBC counts (hematocrit) and hemoglobin concentration and increased white blood cell counts were observed in the high-concentration group at 12 and 18 months in both males and females. These and other hematology parameters were not consistently observed in other exposure groups. Urinalysis and clinical chemistry results showed no consistent exposure-related effects. A concentration-related increase in the number of rats found dead or killed in extremis was observed. Increased mortality occurred in animals exposed to 50, 250, and 1250 ppm. No statistical analysis of the mortality data was reported. Much of the early mortality was associated with increased incidence of cancer that resulted from vinyl bromide exposure. There was also a concentration-related decrease in body weight that exceeded 10% of the control weight in the animals exposed to 50, 250, and 1250 in both males and females. Body weight in the groups exposed to 10 ppm were slightly decreased (3-5%). Increases in relative liver weight of approximately 20% were observed in males at 6 months of exposure in all exposed groups and at 12 months of exposure at 50 ppm or greater (Huntington Research Center, 1977a). Liver weights continued to be elevated at 18-

months exposure to 1250 ppm and at 18- and 24-months exposure to 250 ppm in both male and female rats, but these results are confounded by the high incidence of liver neoplasms in these groups. Increased spleen weight was observed at 6 and 12 months in the two highest exposure groups in males and in the highest exposure concentration in females, but was not found to be affected at 18 or 24 months.

Histopathological results are reported for 6 and 12 months by Huntington Research Center (1977b), for 18 months by Busey (1978), and for the terminal sacrifice by Busey (1979) and Benya et al. (1982). No consistent exposure-related gross or microscopic alterations were observed in any tissues examined from rats exposed for 6 months. However, dose-related increases in neoplastic and nonneoplastic lesions of the liver were observed at all exposure concentrations in animals exposed for 12, 18, and 24 months. At the 6-month sacrifice, focal fibrosis of the heart was seen in 1/15, 0/3, 5/13, 7/13, and 11/25 males and in 0/12, 0/1, 1/12, 2/17, and 4/23 females exposed to 0, 10, 50, 250, and 1250 ppm vinyl bromide, respectively. Histopathological lesions of the heart were not observed at other time points. After exposure to 250 or 1250 ppm, cortical nodules of the adrenal gland were elevated in males and females at 6 and 18 months, respectively.

Histopathological lesions of the liver were minimally increased at 12 months, but were consistently increased at 18 and 24 months. At 18 months, eosinophilic foci and basophilic foci were increased in groups exposed to 50, 250, and 1250 ppm. Focal hypertrophy and peliosis (atelectasia) were increased in all exposed groups. Bile duct proliferation was also slightly increased in all exposed groups. In male rats examined at the terminal sacrifice, eosinophilic foci were seen in 19, 42, and 39% of control, 10-ppm and 50-ppm animals, respectively. Basophilic foci were seen in 12, 31, and 39%, and clear cell foci were seen in 1, 12, and 25% of animals in the control, 10-ppm and 50-ppm groups, respectively (n = 74, 52, and 28, respectively). Similar results were obtained when animals dying during the last 6 months of the study were included with the terminal sacrifice. No exposure-related nonneoplastic histopathology was observed in sites other than the liver at the terminal sacrifice. Incidences of these lesions in the groups exposed to 250 and 1250 ppm were lower than in the controls, but the interpretation of this finding is confounded by the high incidence of neoplasms in these groups, the early termination of the 1250-ppm group, and the small numbers of animals surviving to terminal sacrifice for which livers were examined (n = 6 and 19 for the 250- and 1250-ppm groups, respectively).

Vinyl bromide was a potent carcinogen under the conditions of this study. Angiosarcomas of the liver occurred in 7, 36, 61, and 43 males and in 10, 50, 61, and 41 females exposed to 10, 50, 250, and 1250 ppm, respectively (n = 120). Neoplasms derived from hepatocytes were also observed. Combined hepatocellular carcinoma and neoplastic nodule were found in 4, 5, 11, 11, and 5% of the groups exposed to 0, 10, 50, 250, and 1250 ppm vinyl bromide, respectively. The occurrence of a cancer response may confound the interpretation of nonneoplastic responses in

the same tissue because it is not clear whether the response is preneoplastic (i.e., an early indication of a neoplastic process) or independent of the occurrence of tumors. Although the incidence of total liver neoplasms was higher than the incidence of the nonneoplastic lesions, the interpretation of the nonneoplastic lesions is not confounded because of the relatively low incidence of hepatocyte-derived tumors. Altered hepatocellular foci, such as those observed in this study, are sometimes thought to be an early stage in the progression to cancer, but it is thought that very few of these foci actually progress to cancer, and when the toxicant exposure is stopped, these foci can regress. The incidence of nonneoplastic lesions involving the hepatocytes was higher than that of hepatocyte-derived neoplasms in a lifetime study, indicating that the lesion does not necessarily progress to cancer during a lifetime. Under these circumstances, it is appropriate to consider the nonneoplastic response independently of the cancer response. This study therefore identifies a LOAEL for noncancer effects in the liver at 10 ppm [LOAEL(ADJ) and LOAEL(HEC) = 7.7 mg/cu.m].

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 is used for protection of sensitive human subjects. An uncertainty factor of 3 is used for interspecies extrapolation. A full factor of 10 is not necessary for interspecies extrapolation due to the application of dosimetric adjustments. An uncertainty factor of 10 is used to extrapolate from a LOAEL to a NOAEL. An uncertainty factor of 10 is applied for database deficiencies, including lack of data for a second species, and lack of any developmental or reproductive toxicity data.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

Newborn rats, together with their mothers, were exposed to 0 or 2000 ppm (0 or 8744 mg/cu.m) vinyl bromide vapor (Bolt et al., 1979) for 8 hours/day and 5 days/week (duration adjusted to 0 or 2082 mg/cu.m). Exposure lasted from 8 to 15 weeks. Rats were sacrificed at 8, 10, 12, and 15 weeks, and livers were examined for preneoplastic foci of hepatocellular nucleoside-5'-triphosphatase (ATPase) deficiency. ATPase-deficient foci were found to increase with length of exposure. No control data were presented, and no statistical analyses were done. A LOAEL of 2000 ppm for liver effects can be determined from these data.

Acute and subacute studies support the liver as the primary target organ following inhalation exposure to vinyl bromide (Leong and Torkelson, 1970). Exposures to 50,000 ppm (218,818 mg/cu.m) resulted in unconsciousness in 25 minutes and death in 7 hours (Dow Chemical Company, unpublished data; as cited in Leong and Torkelson, 1970). Rats surviving exposure to 50,000 ppm for 1.5 hours showed slight to moderate liver and kidney damage on necropsy

conducted 2 weeks after exposure. Other effects observed following exposure to relatively high concentrations of vinyl bromide vapors include neurological and kidney effects, and death. Acute inhalation of 100,000 ppm (437,636 mg/cu.m) vinyl bromide resulted in deep anesthesia and death in rats in about 15 minutes. Groups of 5 male Wistar rats were exposed to 10,000 ppm vinyl chloride for 7 hours/day, 5 days/week for exposure durations of 3 days and 1, 2, and 4 weeks. This exposure resulted in hypoactivity and drowsiness during each day of the exposure, with a rapid recovery after exposure ceased. Significantly decreased body weights after 3 and 4 weeks of exposure were observed. No exposure- related histopathology was observed.

In a subchronic study (Leong and Torkelson, 1970), groups of 60 rats, 6 rabbits, and 6 monkeys (half males and half females except for the monkey control group, which had 4 females) were exposed for 6 hours/day, 5 days/week to 250 or 500 ppm vinyl bromide for 6 months (duration adjusted to 200 and 380 mg/cu.m, respectively). The results of this study showed no statistically significant exposure-related adverse effects in rats, rabbits, or monkeys. Parameters monitored included clinical symptoms, body weight, food consumption (rats and rabbits only), hematology, blood bromide concentration, organ weights, gross pathology, and histopathology (thyroid, lungs, heart, liver, pancreas, spleen adrenals, kidneys, and gonads). Inhalation studies of vinyl chloride also reported the liver to be a sensitive target for both cancer and noncancer endpoints. Angiosarcomas are also a primary cancer caused by vinyl chloride, and hepatocellular hypertrophy, altered hepatocellular foci, and degeneration are noncancer endpoints observed in vinyl chloride exposed animals. A single subchronic study of vinyl chloride exposure that examines the nose histologically is available. This study found nasal epithelial degeneration in exposed animals at a concentration much higher than the LOAEL for liver effects in other studies, suggesting that nasal effects are not the most sensitive endpoint. However, a NOAEL was not identified. The nasal cavity has not been examined in any inhalation studies of vinyl bromide.

Studies of the kinetics and metabolism of vinyl bromide show that it is metabolized by a saturable pathway to form a reactive metabolite that is capable of alkylating proteins and nucleic acids. Using gas uptake studies in a closed system, Andersen et al. (1980) calculated a V_{max} of 2.1 mg/kg/hour and an apparent inhalation K_m of 18 ppm. Gargas and Andersen (1982) performed gas uptake studies on rats and concluded that there are two distinct saturable components of vinyl bromide metabolism. A low affinity pathway was also identified with $K_m = 11,700$ ppm and $V_{max} = 9.3$ mg/kg/hour. A calculation based on gas uptake studies by Filser and Bolt (1979) showed a saturation concentration of 55 ppm vinyl bromide. These kinetic studies indicate that the metabolism in the range of concentrations used in the principal study is saturable and that in the range of 50 to 1000 ppm, the total amount metabolized might be fairly constant as a result of being above the saturation concentration of the high affinity pathway and far below the K_m of the low affinity pathway. It is noted that the kinetic experiments were done in Wistar (Filser and Bolt, 1979) and Fischer 344 (Andersen et al., 1980) rats and not in Sprague-

Dawley rats, which were used in the Benya et al. (1982) study. The interstrain differences in metabolism are not known, although the results from the two strains used in the kinetic studies seem to agree reasonably well. Bolt et al. (1980) demonstrated protein binding of ¹⁴C-labeled vinyl chloride in the livers of rats exposed in closed chambers to initial concentrations of 15, 120, and 320 ppm vinyl chloride. They showed that the amount bound was a constant proportion of the amount metabolized across this range of concentrations. There is also some evidence for suicide inhibition of cytochrome P-450-dependent activation of vinyl bromide. Exposure of rats to 20,000 ppm vinyl bromide vapor for 4 hours/day for 10 days caused a slight weight depression and a 25% decrease in cytochrome P-450 (Drew et al., 1976). This phenomenon has not been explored further and it is not known whether this could play a significant role in a chronic exposure to low levels of vinyl bromide.

No studies of the reproductive or developmental toxicity of vinyl bromide have been located. Studies of vinyl chloride exposure in rats have found reduced fertility in exposed males and testicular effects, suggesting the possibility of reproductive effects, but no multigeneration reproductive study of vinyl chloride has been reported. No testicular effects were reported in the subchronic study of Leong and Torkelson (1970), but details regarding the testicular histology were not provided.

I.B.5. Confidence in the Inhalation RfC

Study — Medium

Database — Low

RfC -- Low

The confidence in the study was considered to be medium because of the lack of consistency across duration and concentration in the effects, and because a NOAEL was not identified. The confidence in the database is low because of the lack of developmental or reproductive toxicity studies and lack of a chronic study in a second species. The database also lacks adequate evaluation of possible nasal or testicular effects. The resultant confidence in the RfC is low.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1984

Agency Work Group Review — 02/10/1993

Verification Date — 02/10/1993

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for vinyl bromide conducted in August 2003 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or 202-566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Vinyl bromide
CASRN — 593-60-2

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Vinyl bromide
CASRN — 593-60-2

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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U.S. EPA. 1984. Health and Environmental Effects Profile for Bromoethene (Vinyl Bromide). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA-600/X- 84-143.

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Vinyl bromide
CASRN — 593-60-2

Date	Section	Description
05/01/1993	I.B.	Inhalation RfC on-line
10/28/2003	I.B.6	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Vinyl bromide

CASRN — 593-60-2

Last Revised — 03/01/1993

- 593-60-2
- Bromoethene
- Bromoethylene
- Ethene, bromo-
- ETHYLENE, BROMO-
- Vinyl bromide
- BROMURE de VINYLE [French]
- Bromuro de vinilo [Spanish]
- HSDB 1030
- Monobromoethylene
- NCI-C50373
- VINILE (BROMURO DI) [Italian]
- VINYL BROMIDE, inhibited
- Vinylbromid [German]
- VINYLE (BROMURE DE) [French]